

REMARKS

Claims 20-21, 62-67, 69, 71, 76-78, 80-93 are pending and stand rejected. Applicant gratefully acknowledges the withdrawal of rejections and objections not set forth in the Office Action of January 27, 2006.

The Title has been amended to more accurately reflect the subject matter of the pending claims. Claim 76 has been amended to depend from claim 62 rather than cancelled claim 72. No new matter has been added.

Applicant also submits a copy of an alignment of the *Arabidopsis* Met1 and *Zea mays* orthologous sequences, and apologizes for the inadvertent failure to provide a copy of the alignment with the prior response.

Applicant earnestly solicits reconsideration and allowance of claims 20-21, 62-67, 69, 71, 76-78 and 80-93 in view of the amendments and remarks in this Response.

Information Disclosure Statement

Applicant respectfully notes that the Examiner did not initial the patents listed on the PTO-1449 form filed February 25, 2005. Thus, Applicant respectfully requests that the Examiner consider the patents cited in this PTO-1449 and return an initialed copy. For the Examiner's convenience, a copy of the PTO-1449 form filed February 25, 2005, is attached hereto.

Claim Objection

The Examiner objected to claim 76 for depending from a rejected base claim. Applicant believes that the objection is intended to address the dependency of claim 76 from a cancelled base claim. Assuming this to be the case, Applicant has amended claim 76 to depend from claim 62. The Examiner is requested to withdraw the objection to claim 76 in view of the correction to claim dependency.

Rejection Under 35 § 112, Second Paragraph

The Examiner rejected claims 20 and 62 for the recitation of “a sequence whose transcription product comprises a partial or full length *Arabidopsis* DNA methyltransferase 1 (Metl) sequence.” Office Action at page 3. The Examiner stated that since Accession No. L10692 is a DNA sequence, “it is unclear how a transcription product can be a DNA sequence and not a mRNA sequence.” Office Action at page 3. Applicant respectfully traverses.

It is well known in the art that a transcription product is RNA. It is also well known in the art that a transcription product is a faithful copy of the DNA template from which the transcription product was transcribed. Therefore, it would be clear to one of ordinary skill that the transcription product of the *Arabidopsis* DNA methyltransferase 1 (Metl) sequence would be an RNA sequence. The Examiner is requested to withdraw the rejection of claims 20 and 62 under 35 § 112, second paragraph for indefiniteness.

Written Description Rejection Under 35 § 112, First Paragraph

The Examiner rejected claims 20-21, 62-67, 69, 71, 76-78, 80-93 under 35 § 112, first paragraph, for lack of written description.

The Examiner asserted that “Applicants do not disclose any sequence whose transcription product is a partial or full length *Arabidopsis* Metl or *Zea mays* orthologous sequence to the *Arabidopsis* Metl sequence. Applicants do not identify essential and/or unique regions of the *Arabidopsis* Metl sequence, nor any partial sequences thereof, nor any partial or full sequences of the *Zea mays* homologue of the *Arabidopsis* Metl sequence, that can be used to down-regulate one or more methylating enzymes present in a plant.” Office Action at page 5. The Examiner asserted that the Applicant failed to meet either prong of the two-prong test set forth by Lilly. Office Action at page 6. The Examiner asserted that the Applicant failed to describe a representative number of sequences whose transcription product is a partial or full length *Arabidopsis* Metl sequence or *Zea mays* homologue, and failed to describe structural features common to members of the claimed genus of polynucleotides. Office Action at pp. 5-6. The Examiner also asserted that Applicant has only disclosed “a nucleic acid sequence that encodes a full-length *Arabidopsis* Metl protein that is effective in down-regulating the corresponding endogenous gene when transformed in *Arabidopsis* or in *Brassica campestris* and *Brassica*

oleraceae (see below for details).” The Examiner also asserted that Applicant has not disclosed “a full length Metl sequence that can down-regulate any methylating enzyme.” Office Action at page 7.

Applicant respectfully traverses for reasons of record and the following reasons.

Written description is a question of fact, judged from the perspective of one of ordinary skill in the art as of the relevant filing date. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Compliance with § 112 requires sufficient information in the specification to show that the inventor possessed the invention at the time of that original disclosure. See Vas-Cath, 935 F.2d at 1563-64 (“[T]he applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.”); Union Oil Co. of Cal. v. Atl. Richfield Co., 208 F.3d 989, 997 (Fed. Cir. 2000) (“The written description requirement does not require the applicant ‘to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.’” (citation omitted)). The written description requirement may be satisfied “if in the knowledge of the art the disclosed function is sufficiently correlated to particular, known structure.” Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2002).

The Court of Appeals for the Federal Circuit has recognized that disclosure of specific sequences is not a *per se* requirement for satisfying written description. The Court stated in Capon v. Dudas that “[w]hen the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh.” Capon v. Eshhar v. Dudas, 03-1480, 1481 at 15 (Fed. Cir. Aug. 12, 2005).

More recently, the Federal Circuit has held that “(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met [] even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.” Falkner v. Inglis, 448 F.3d 1357, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006). In particular, the Federal Circuit held in Falkner with respect to point (3) that “where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here “essential genes”), satisfaction of the written

description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences.” Id. at 448 F.3d 1368.

The Federal Circuit decisions in Capon and Falkner clearly explain that it is not a *per se* rule that an applicant must recite known structures in order to satisfy the written description requirement. Thus, it is not a *per se* requirement that partial *Arabidopsis* Met1 or *Zea mays* orthologous sequences be recited in the specification. With respect to the present application, the complete *Arabidopsis* Met1 sequence was known as of the earliest priority date of the present application. See, Genbank Accession Number L10692 in the accompanying supplemental Information Disclosure Statement. The complete carrot, corn, pea and tomato Met1 sequences were known of the earliest priority date. See, Genbank Accession Numbers AF007807, AF063403, AF034419 and AJ002140 in the accompanying supplemental Information Disclosure Statement. Thus, accessible literature clearly provided Met1 nucleotide sequences as of the relevant date. One of ordinary skill would have been aware that Met1 nucleotide sequences have a high degree of sequence identity and that there are regions that are highly conserved. See, e.g., Finnegan et al., *Ann. Rev. Plant Physiol. Plant Mol. Biol.* 49:223-247 at pages 227-229. An example is found in the attached diagram, which shows an alignment of DNA methyltransferase sequences from *Arabidopsis* and *Zea mays*. The overall nucleotide sequence identity between the *Arabidopsis* and *Zea* sequences is about 64%. Moreover, there are numerous regions in these sequences that have greater than 75% identity. See, e.g., nucleotides 731 to 856 (76% identity), nucleotides 3329 to 3981 (82% identity), 3635 to 3720 (91% identity), and nucleotides 4331 to 4590 (82% identity). These are strikingly high percent identities given that *Arabidopsis* is a dicot and *Zea* is a monocot.

In addition, a reading of the present specification from the perspective of one of ordinary skill clearly demonstrates that the Applicant was in possession of the claimed invention. The instant specification states in the context of decreasing the degree of methylation that “one can use antisense sequences, e.g., the Met1 as ‘gene’. In addition, it has been found that incorporation of whole or partial copies of an already present gene can result in suppression of gene expression.” Specification at page 18, lines 23-30. The instant specification indicates that “[e]xpression of the MET1 gene can be reduced in the female or male germ lines by employing techniques known in the art. For example MET1 down-regulation can be achieved by expressing

antisense MET1 or antisense MET1 fragments or sense MET1 or partial sense MET1 or ribozymes directed against MET1 or combinations of the preceding, from promoters expressed in the required germ-line. Below is an example of an antisense MET1 approach.” Specification at page 30, lines 15-19. The specification (Examples 3-4) goes on to describe the preparation of a construct having a partial *Arabidopsis* Met1 antisense sequence targeted to the female germ line and its use to produce modified endosperm. Specification at page 32, lines 1-28.

Rather than mechanically reciting partial *Arabidopsis* Met1 or *Zea mays* orthologous sequences in the specification, Applicant here referred to partials of known sequences, the *Arabidopsis* Met1 or *Zea mays* orthologous sequences. As the Federal Circuit has said, “[c]ertainly no length requirement exists for a disclosure to adequately describe an invention. . . . [T]he adequacy of the description . . . depends on its content in relation to the particular invention, not its length.” See In re Hayes Microcomputer Products, Inc. Patent Litigation (Ven Tel, Inc. v. Hayes Microcomputer Products, Inc.), 982 F.2d 1527 (Fed. Cir. 1992). Accordingly, as the standard for written description is assessed from the viewpoint of one having ordinary skill in the art, the specification provides more than adequate written description for the recitation of a partial *Arabidopsis* Met1 or *Zea mays* orthologous sequence.

The Examiner interpreted the word “partial” in the claims to comprise “any two consecutive amino acids from *Arabidopsis* or *Zea mays* DNA methyltransferase 1 (Met1) protein” and asserted that “Applicant has not disclosed any partial sequence as the Office interprets ‘a partial’ sequence, nor has Applicant disclosed any *Zea mays* homologous Met1 sequence.” Office Action at page 7. The Examiner also indicated that “partial sequence reads on any two nucleotides from applicants’ Met1 sequence.” Office Action at page 10.

The written description requirement is viewed from the perspective of one of ordinary skill in the art as of the relevant filing date. Vas-Cath, Inc., supra. A Declaration under 37 CFR § 1.132 by Dr. Steven Jacobsen (hereinafter, the “Jacobsen Declaration”) accompanies this Response. Dr. Jacobsen has conducted research in the genetics of DNA methylation patterning in *Arabidopsis* and genome wide analysis of DNA methylation since 1997, and thus is qualified to discuss the genetics and biochemistry of DNA methylation in plants. As stated in the Jacobsen Declaration, one of ordinary skill in the art would not have interpreted a partial *Arabidopsis* Met1 or *Zea mays* orthologous sequence as used in the claims to comprise only two

consecutive nucleotides from the *Arabidopsis* Met1 or *Zea mays* sequences. One of ordinary skill would have known that sequences having only 2 nucleotides of sequence identity are too short to stably hybridize to a complementary sequence such that downregulation can occur. Jacobsen Declaration at paragraphs 10-11. That is, the Examiner's interpretation of "partial" does not correspond to the interpretation that would have been given by one of ordinary skill. The interpretation of a claim must be consistent with the interpretation that would be given by one of ordinary skill in the art. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). Applicant also refers to the construct having an *Arabidopsis* MET1 antisense sequence targeted to the female germ line and described in Examples 3 and 4, which is less than full-length.

In summary, it is not a *per se* rule that numerous partial sequences of known Met1 genes must be recited in the specification in order to satisfy the written description. There is accessible literature providing Met1 nucleotide sequences, there is a clear description in the specification, and there is the construction and use of a partial sequence for downregulating a Met1 in the specification. One of ordinary skill would have clearly recognized Applicant had possession of what is now claimed. The Examiner is requested to withdraw the rejection of claims 20-21, 62-67, 69, 71, 76-78, 80-93 for lack of written description under 35 U.S.C. §112, first paragraph.

Enablement Rejection Under 35 § 112, First Paragraph

The Examiner rejected claims 20-21, 62-67, 69, 71, 76-78, 80-93 under 35 § 112, first paragraph, for lack of enablement.

Applicant respectfully traverses for reasons of record and the following reasons.

Enablement requires that the specification teach those in the art how to make and use the invention without 'undue experimentation.' See *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). After a response by an applicant, the examiner "must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence." MPEP § 2164.04.

The Examiner asserted that the “state-of-the-art teaches down-regulating methylating genes produces unpredictable results” and referred to an article by Jacobsen et al (2000) to support this assertion. Office Action at page 10. The Examiner asserted that the Jacobsen 2000 reference is “a perfect reference illustrating the unpredictability of the claimed techniques” and that Jacobsen et al. discloses “the totally unexpected result that another sequence of DNA is hypermethylated.” Office Action at page 13. (Emphasis in original).

First, the observation concerning the *SUPERMAN* gene was reported in 1997. See, Jacobsen Declaration at paragraph 12. Thus, it was already known in 1999 that the *SUPERMAN* gene was hypermethylated in *Arabidopsis* lines expressing a Met1 antisense construct and exhibiting up to 90% overall hypomethylation. Dr. Jacobsen is the first author of the Jacobsen 1997 and 2000 articles, and is familiar with the literature regarding the genetics and biochemistry of DNA methylation in plants. Jacobsen Declaration at paragraphs 7 and 13. According to Dr. Jacobsen, the observation of hypermethylation of the *SUPERMAN* gene or the *AGAMOUS* gene in an *Arabidopsis* Met1 antisense construct-containing line does not change the fact that this line had a significant reduction in the degree of overall DNA methylation. The data about the *SUPERMAN* and *AGAMOUS* genes in the Jacobsen 1997 and 2000 references have no bearing on whether one of ordinary skill would have expected a decrease in the degree of overall DNA methylation upon downregulation of Met1 expression. Jacobsen Declaration at paragraph 14.

Second, the Examiner has failed to identify a single instance where downregulation of a Met1 gene failed to reduce the degree of methylation. The Examiner acknowledges that Jacobsen et al. also note that *Arabidopsis* Met1 antisense lines had a 80-90% decrease in the degree of overall DNA methylation. Office Action at page 10.

The Examiner interpreted claims 20 and 62 broadly to mean “a construct comprising a promoter and another sequence, wherein the sequence is located in a position not necessarily next to the promoter. Therefore, the promoter would not affect the transcription of the sequence.” (Emphasis in original). Office Action at page 10.

Claims are to be given their broadest reasonable interpretation during prosecution. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). However, the interpretation must be consistent with the interpretation that would be given to the claims by one of ordinary skill in the art. In re Cortright, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed.

Cir. 1999). Here, the specification describes how downregulation can be achieved by expressing Met1 sequences from promoters expressed in the required germ line. Specification at page 30, lines 15-19. As indicated in the Jacobsen Declaration, one of ordinary skill would have considered the Examiner's interpretation of claims 20 and 62 in view of the specification to be unreasonable. One of ordinary skill would have interpreted these claims to mean that a promoter that targets expression to female germ line cells drives transcription of the indicated Met1 sequence. Jacobsen Declaration at paragraph 15.

The Examiner interpreted the word "partial" in the claims to comprise "any two nucleotides from applicants' Met1 sequence." Office Action at page 10. As discussed above, one of ordinary skill in the art would not have considered two consecutive nucleotides as being a partial *Arabidopsis* Met1 or *Zea mays* orthologous sequence. Jacobsen Declaration at paragraphs 10-11.

The Examiner asserted that "Applicants have not disclosed how one makes or isolates any of the other sequences that are encompassed by Applicants' broad claims." Office Action at page 10. The Examiner also asserted that "Applicants have not taught which regions of the respective polynucleotides can be used to amplify, for example, the *Zea mays* orthologous sequence, or which regions can be used as a probe to isolate any of said polynucleotide sequences." Office Action at page 10.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is undertaken, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The Examiner's requirement for recitations of partial *Arabidopsis* Met1 or *Zea mays* orthologous sequences misplaces the focus of the enablement inquiry on the length of the disclosure rather than its substance. As the Federal Circuit has held, "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." See DeGeorge v. Bernier, 768 F.2d 1318 (Fed. Cir. 1985) and cases cited therein. Indeed, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." See In re Wright, 999 F.2d 1557 (Fed. Cir. 1993).

The general principles of downregulation technologies would have been well known to one of ordinary skill. In the case of antisense technology, see, e.g., U.S. 6,940,001, U.S.

6,900,368, U.S. 6,897,359, U.S. 6,455,688, U.S. 6,355,862 and U.S. 6,329,567. It would have been known to one of ordinary skill that antisense constructs complementary to at least a portion of the messenger RNA for Met1 can be constructed that hybridize with the corresponding mRNA and interfere with expression. See van der Krol et al., Biotechniques 6:958-976(1988). Antisense inhibition has been shown using either full-length or partial cDNA. See, e.g., Sheehy et al., Proc. Natl. Acad. Sci. USA 85:8805-8809 (1988); Cannon et al., Plant Mol. Biol. 15:39-47 (1990). One of ordinary skill would have also known that 3' non-coding sequences (Ch'ng et al., Proc. Natl. Acad. Sci. USA (1989) 86:10006-10010) and fragments of 5' coding sequence, (Cannon et al., Plant Mol. Biol. (1990) 15:39-47), can be used. One of ordinary skill would have been aware that antisense constructs were, in general, successful in achieving downregulation. See, e.g., the Bourque 1995 reference in the accompanying supplemental IDS.

In the case of sense suppression, one of ordinary skill would have been aware that sense constructs were, in general, successful in achieving downregulation. See, e.g., the Elkind, Faske and Trevanian references in the accompanying supplemental IDS.

The complete sequences of the *Arabidopsis* Met1 and *Zea mays* orthologous sequences were known as of the earliest priority date of the present application. See, e.g., Genbank Accession Numbers AF063403 and L10692. L10692 is in the accompanying supplemental Information Disclosure Statement. It would have been a routine matter for one of ordinary skill to screen and identify satisfactory downregulation constructs. For example, techniques such as constructing DNA containing partial or full-length *Arabidopsis* or *Zea mays* DNA methyltransferase 1 Met1 sequences, constructing plant transformation vectors, transforming plants, and screening for overall DNA methylation status would have been typical of those carried out by one of ordinary skill. See Jacobsen Declaration at paragraph 16.

Since the general principles of downregulation technologies were known, since the complete sequences of the *Arabidopsis* Met1 and *Zea mays* orthologous sequences were known, and since methodologies for screening plants having partial *Arabidopsis* Met1 and *Zea mays* sequences for a decrease in the degree of overall DNA methylation were known, one of ordinary skill would have required no more than routine experimentation to practice the full scope of the pending claims.

The Examiner referred to an article by Fourgoux-Nicol et al. and asserted that the reference was used “to show that protocols that use ‘standard’ techniques, which in this case are hybridization reactions used to isolate nucleic acid sequences, do not always produce expected results. This reference was used to demonstrate unpredictability in the art.” Office Action at page 14. The Examiner also asserted that using the mechanism of sense suppression to reduce expression of the endogenous corresponding gene produces unpredictable results and referred to an article by Gutterson. Office Action at page 11. The Examiner also asserted that “antisense molecules that exhibit less than 100% sequence identity to the target sequence produce unexpected results” and referred to an article by Emery et al. Office Action at page 12.

The Examiner’s position appears to be that these three articles evince the state of the art in downregulation technologies, including the use of sequences having less than 100% identity to an endogenous gene, as of the earliest priority date. However, the references cited by the Examiner do not demonstrate non-enablement of the pending claims, but in fact support enablement. These references demonstrate a high level of skill in the art for down regulation technologies such as antisense and cosuppression, and that those of ordinary skill knew how to make and use sequences for downregulation. The references demonstrate that use of these technologies required, at most, routine experimentation. Courts have noted that in fields such as this, where the art typically engages in experimentation, even complex experimentation is not necessarily undue. See, e.g., In re Certain Limited-Charge Cell Culture Microcarriers 221 USPQ 1165, 1174 (Int’l Trade Comm’n 1983), aff’d. sub nom. Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

The Fourgoux-Nicol reference reports that nucleic acids that do not have 100% DNA sequence identity can hybridize to each other. This fact would indicate to one of ordinary skill that hybridization would likely occur between a partial or full length *Arabidopsis* or *Zea mays* DNA methyltransferase 1 Met11 sequence and an endogenous DNA methyltransferase 1 Met1 target even when there is less than 100% sequence identity. Jacobsen Declaration at paragraphs 17-20.

In addition, other publications show that the use of heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene, were known to be successful in achieving downregulation of the endogenous gene. Copies of the publications listed

below are in the accompanying supplemental IDS. Elkind et al. report that introduction of a bean phenylalanine ammonia-lyase (PAL) sense sequence into tobacco resulted in reduced levels of PAL activity and reduced accumulation of endogenous PAL transcripts. See pages 9059-9060 of Elkind, Y., et al. (1990). Proc Natl Acad Sci U S A 87(22): 9057-61. Hibino et al. report that introduction of an *Aralia cordata* cinnamyl alcohol dehydrogenase (CAD) antisense construct into tobacco resulted in an approximately 20-55% reduction in CAD activity. Hibino T., et al. (1995) Biosci. Biotec. Biochem 59:929-931. Bolitho et al. report that introduction of an apple antisense ACC-oxidase reduced the level of RNA and the activity of the corresponding gene in tomato. Figures 3 and 4 of Bolitho, K. M., et al. (1997) Plant Science 122: 91-99. Salehuzzaman et al. report that introduction of a cassava granule bound starch synthase antisense gene suppressed levels of the corresponding protein in potato. Figure 10 in Salehuzzaman, S. N., et al. (1993) Plant Mol Biol 23(5): 947-62. According to Dr. Jacobsen, one of ordinary skill would have expected that in general heterologous partial or full length sequences can be used to downregulate endogenous genes based on references such as Elkind et al., Hibino et al., Bolitho et al. and Salehuzzaman et al. Jacobsen Declaration at paragraph 21-23.

There are additional references that report downregulation using heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene. Temple et al. report that introduction of an alfalfa glutamine synthetase (GS) antisense sequence into tobacco resulted in decreased GS protein. See Figure 3b of Temple, S. J., et al. (1993). Mol Gen Genet 236(2-3): 315-25.

Oliver et al. report that introduction of a cucumber NADH-dependent hydroxypyruvate reductase (HPR) antisense sequence into tobacco resulted in reduced enzyme activity and HPR protein levels. See Figure 2a of Oliver, M. J., et al. (1993). Mol Gen Genet 239(3): 425-34.

Van der Krol et al., report that introduction of a petunia chalcone synthase (CHS) antisense sequence inhibited expression of the tobacco CHS. Page 868, right column, first paragraph of Van der Krol, A. R., et al. (1988) Nature 333: 866-869.

Carron et al. report that introduction of an *Antirrhinum* dihydroflavonol reductase antisense sequence into birdsfoot trefoil resulted in decreased tannin levels. See Figure 3 of Carron, T. R., et al. (1994). Theoretical and Applied Genetics 87(8): 1006-1015.

Einset reports that introduction of a tomato ACC-oxidase antisense sequence into tobacco was effective in downregulating ethylene production in a tissue-specific manner. See Einset, J. W. (1996). *Plant Cell Tissue and Organ Culture* 46(2): 137-141.

Trevanion et al. report that introduction of a sorghum NADP-malate dehydrogenase sense sequence into the dicot *Flaveria bidentis* resulted in suppression of NADP-MDH activity. See Trevanion, S. J., et al. (1997). *Plant Physiol* 113(4): 1153-1165.

Faske et al. report that introduction of a pea NADP-malate dehydrogenase sense sequence into tobacco was more effective in silencing the corresponding gene than the pea antisense sequence. See page 713, left-hand column of Faske, M., et al. (1997). *Plant Physiol* 115(2): 705-715.

Herbik et al. report that an introduction of an *Arabidopsis* nicotianamine synthase antisense sequence in tobacco resulted in reduction of nicotianamine content and the exhibition of a chloronerva-like phenotype. Herbik, A., et al. (1999). *Eur J Biochem* 265(1): 231-9.

Veena et al. report that introduction of a *Brassica* glyoxalase I (Gly1) antisense sequence into tobacco resulted in reduced Gly1 protein levels. See Figure 6d and page 390, left-hand column, last paragraph, of Veena, et al. (1999). *Plant Journal* 17(4): 385-395.

As stated in Dr. Jacobsen's Declaration, one of ordinary skill would not conclude from the Gutterson reference that use of sense suppression techniques in plant molecular biology requires a 100% sequence match between an introduced sequence and its target. Jacobsen Declaration at paragraphs 26-27. While the Gutterson reference reports that a chrysanthemum chalcone synthase sense sequence did not suppress a petunia chalcone synthase, such a result does not mean that sequences with imperfect homology would necessarily be ineffective for downregulation. For example, bean and tobacco phenylalanine ammonia-lyase (PAL) DNAs have 71% sequence identity. Elkind, et al. (1990) *Proc Natl Acad Sci U S A* 87: 9057-61 at page 9057. Introduction of the bean PAL sense sequence into tobacco resulted in reduced levels of PAL activity and reduced accumulation of endogenous PAL transcripts. Elkind et al. at pages 9059-9060. Based on references such as the Elkind reference, one of ordinary skill would have concluded that sense suppression sequences with less than 100% sequence identity can be used to downregulate a heterologous endogenous gene. Jacobsen Declaration at paragraphs 26-27.

Finally, the Emery reference is a post-filing date reference. In general, post-filing date references are not to be used to demonstrate that an application is non-enabling, unless the post-filing date reference provides evidence of what one skilled in the art would have known on or before the effective filing date. MPEP § 2164.05(a); In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). Here, the Emery reference has no evidence of what one skilled in the art would have known on or before the effective filing date and, therefore, the Emery reference is not relevant to whether the claimed invention would have been enabled as of the effective filing date. The Examiner referred to In re Wright, 999 F.2d 1557 (Fed. Cir. 1993). In contrast to the situation in Wright, the Emery reference has no indication of what one skilled in the art would have known on or before the effective filing date.

Even assuming the Emery reference is relevant, one of ordinary skill would not conclude from the Emery reference that use of antisense techniques in plant molecular biology requires a 100% sequence match between an introduced sequence and its target. While the Emery reference reports that single mismatches within microRNA target sites can abolish miRNA function, such a result does not mean that sequences with imperfect homology would necessarily be ineffective for downregulation. For example, apple and tomato ACC-oxidase cDNAs have 74% sequence identity. Bolitho et al. at page 96, left-hand column. An apple ACC-oxidase antisense construct successfully downregulated the endogenous ACC-oxidase in tomato. Bolitho at Figures 3 and 4. Based on references such as the Bolitho reference, one of ordinary skill would have concluded that antisense sequences with less than 100% sequence identity can be used to downregulate a heterologous endogenous gene. Jacobsen Declaration at paragraphs 24-25. In addition, the Emery reference demonstrates the precision with which one of ordinary skill can upregulate or downregulate a particular gene. Therefore, the Emery reference supports enablement of the presently claimed invention as of the effective filing date.

In summary, the state of the art is not as bleak as the Examiner would make it out to be. Rather, the specification enables one of ordinary skill in the art as of the effective filing date to make and use the claimed methods without undue experimentation, in view of the arguments and references discussed above, and the Declaration of Dr. Steven Jacobsen enclosed herewith. The Examiner is respectfully requested to withdraw the rejection of claims 20-21, 62-67, 69, 71, 76-78, 80-93 under 35 U.S.C. §112, first paragraph, for lack of enablement.

Applicant : Roderick J. Scott
Serial No. : 10/058,825
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Attorney's Docket No.: 11696-067001 / PM32757

Double Patenting

The Examiner provisionally rejected the pending claims under the judicially created doctrine of obviousness type double patenting, in view of claims 36-43, 45-55, 57-69 and 71-73 in US Application No. 10/702,341. Applicant believes that the provisional double patenting rejection is moot in view of the fact that Application No. 10/702,341 is now abandoned. Applicants respectfully request that the double patenting rejection be withdrawn.

Conclusion

In view of the amendments and remarks above, Applicant respectfully requests reconsideration and allowance of claims 20-21, 62-67, 69, 71, 76-78, 80-93. Enclosed is this Firm's Check No. 203767 in the amount of \$1,020 to cover the filing fee for a three-month Petition for Extension of Time. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: July 27, 2006



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